SPECIAL ARTICLE

Weighing the Risks and Benefits of Tamoxifen Treatment for Preventing Breast Cancer

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Background: **In response to findings from the Breast Cancer Prevention Trial that tamoxifen treatment produced a 49% reduction in the risk of invasive breast cancer in a population of women at elevated risk, the National Cancer Institute sponsored a workshop on July 7 and 8, 1998, to develop information to assist in counseling and in weighing the risks and benefits of tamoxifen. Our study was undertaken to develop tools to identify women for whom the benefits outweigh the risks.** ***Methods:*** **Information was reviewed on the incidence of invasive breast cancer and of *in situ* lesions, as well as on several other health outcomes, in the absence of tamoxifen treatment. Data on the effects of tamoxifen on these outcomes were also reviewed, and methods were developed to compare the risks and benefits of tamoxifen.** ***Results:*** **The risks and benefits of tamoxifen depend on age and race, as well as on a woman's specific risk factors for breast cancer. In particular, the absolute risks from tamoxifen of endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis increase with age, and these absolute risks differ between white and black women, as does the protective effect of tamoxifen on fractures. Tables and aids are developed to describe the risks and benefits of tamoxifen and to identify classes of women for whom the benefits outweigh the risks.** ***Conclusions:*** **Tamoxifen is most beneficial for younger women with an elevated risk of breast cancer. The quantitative analyses presented can assist health care providers and women in weighing the risks and benefits of tamoxifen for reducing breast cancer risk. [J Natl Cancer Inst 1999;91:1829–46]**

I. Introduction

The Breast Cancer Prevention Trial (BCPT) was a randomized, placebo-controlled, 6-year study of the effects of tamoxifen (20 mg once daily for up to 5 years) in a population of women at elevated risk of breast cancer. To be eligible for the trial, women had to be 60 years old or to have a projected 5-year risk of invasive breast cancer (IBC) equal to or greater than that of an average 60-year-old woman (1.66%). Women with previous breast cancer or ductal carcinoma *in situ* (DCIS) were excluded from the trial. Women with lobular carcinoma *in situ* (LCIS) who had been treated with lumpectomy and radiation were eligible for the study. On April 6, 1998, the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) released data from the BCPT demonstrating that tamoxifen treatment reduced the risk of incident IBC. Fisher et al. *(1)* subsequently published data from the BCPT showing a 49% reduction in IBC. Similar reductions were seen in all age groups, in each year of the study, and in women who were eligible by virtue of a baseline diagnosis of LCIS. There was also a 50% reduction in the risk of noninvasive incident breast cancer, and the incidence of fractures, including hip fractures, was reduced in subjects receiving tamoxifen *(1)*.

Unfortunately, some women in the BCPT also experienced life-threatening adverse effects from tamoxifen, including excesses of endometrial cancer, pulmonary embolism, stroke, and deep vein thrombosis. Some excess incidence of cataracts was also noted.

The variety of effects from tamoxifen complicates the decision to use it in prevention. A good decision will depend on the particular risk profile of the woman and on her preferences. The balance of benefits and adverse effects from tamoxifen depends on age and on other factors, such as the woman's underlying risk of breast cancer and whether she has had a hysterectomy. The NCI held a workshop on July 7 and 8, 1998, to develop information to assist women and their health care providers in deciding whether or not to initiate preventive use of tamoxifen (*see* "Appendix: Workshop Program and List of Participants" section appearing before "References"). While this information would be based on the results of the BCPT whenever possible, workshop participants were also asked to consider the potential benefits and risks for high-risk women who were not eligible for the BCPT, such as women with DCIS.

This special article is based in part on the presentations and discussions at this workshop as well as on additional statistical analyses of risk/benefit indices and additional review of the literature.

Shortly after the workshop, reports from two smaller controlled studies *(2,3)* appeared that did not demonstrate a reduction in breast cancer incidence from tamoxifen use. Although the risk/benefit tables that we present are based solely on BCPT estimates of tamoxifen's effects, we discuss the impact of including data from other studies.

II. Projecting Risks in the Absence of Tamoxifen Treatment

To assess the risks and benefits of tamoxifen, it is necessary to know the incidence rates for certain health outcomes in the

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absence of tamoxifen. Except for cataracts, we relied on data from outside the BCPT to estimate background incidence rates, although estimates of the effects of tamoxifen on these rates were obtained from BCPT data alone. Risks and benefits were calculated by comparing estimated incidence rates in the presence and absence of tamoxifen. We now review information on the methods used to estimate incidence rates in the absence of tamoxifen.

A. Breast Cancer

1) Invasive Breast Cancer (IBC)

The primary end point of the BCPT was IBC. To be eligible for the BCPT, a woman had to be 60 years old or to be 35–59 years old with a projected 5-year risk of IBC of at least 1.66%, which is the rate for an average 60-year-old white woman in the United States. We, therefore, emphasize estimates of 5-year risks of IBC in organizing our risk/benefit tables.

We recommend the method used in the BCPT for calculating the projected 5-year risk of IBC for a woman with particular risk factors but with no history or current evidence of invasive cancer, DCIS, or LCIS. The method is based on the earlier work of Gail et al. *(4)*, who analyzed data from the Breast Cancer Detection Demonstration Project (BCDDP) and developed a model for projecting total breast cancer incidence, including both invasive and *in situ* lesions. The model of Gail et al. *(4)* uses the age of the counselee and the following additional risk factors: number of affected first-degree relatives, age at menarche, age at first live birth, number of previous breast biopsies, and the presence of atypical hyperplasia in a biopsy specimen. Benichou *(5)* wrote a computer program, RISK, that allows one to estimate the absolute risk of developing breast cancer for a woman of any age from 20 to 80 years and with any pattern of these risk factors over any desired time interval. This model was intended for women in a program of annual screening with mammography. Although the model overpredicts risk in young unscreened women *(4,6–8)*, it accurately predicted total breast cancer incidence for women under age 60 years in the placebo arm of the BCPT and underestimated total breast cancer incidence somewhat for women over age 59 years *(9)*. The BCPT protocol specified annual mammography and semiannual breast examinations for all women in the trial.

NSABP statisticians, including Stewart J. Anderson and Carol K. Redmond, modified the model of Gail et al. to project only IBC *(10)*. While retaining the relative risk features of the model by Gail et al., they employed composite age-specific rates of IBC for white women from the Surveillance, Epidemiology, and End Results (SEER) Program[1] of the NCI, instead of the composite rates from the BCDDP used by Gail et al., and they modified the factors needed to convert composite rates to baseline rates accordingly. In addition, NSABP statisticians adapted the model to project risks for black women by using age-specific composite SEER rates for black women and by modifying the factors used to convert composite rates to baseline rates. Apart from black women, the same projections were made for all other U.S. women as for whites.

The ratio of age-adjusted rates of IBC comparing Hispanic women with non-Hispanic white women in the United States is 0.60 *(11)*. Because we did not have data on the prevalence of breast cancer risk factors among Hispanic women, we could not modify the IBC risk model for Hispanic women. It is likely, however, that the rates of IBC predicted for white women by the IBC risk model overestimate the correct rates for Hispanic women.

The placebo arm of the BCPT, exclusive of women with LCIS at baseline, affords an excellent opportunity to test the projections of the modified risk model for invasive cancer for women in regular screening. The agreement of observed and expected incident invasive cancers is excellent for all ages (Table 1). Because only 1.7% of the BCPT participants were black, however, no independent validation was possible for black women. In fact, 1.7 cases were predicted among black women, and two cases were observed. Even though the model predicted well for all ages, there is some evidence that the model underpredicts risk slightly for those in the lowest quintile of projected risk (observed-to-expected ratio = 0.70; 95% confidence interval [CI] = 0.47–1.11) and overpredicts risk slightly for those in the highest quintile (observed-to-expected ratio = 1.21; 95% CI = 0.92–1.64). Costantino et al. *(9)* provide additional information on the validity of these projections.

A computer program designed to help health care providers estimate the risk of IBC and discuss the use of tamoxifen for chemoprevention with their patients is available through the NCI's Cancer Information Service (telephone No. 1-800-4-CANCER or Web site http://cancerTrials.nci.nih.gov). Alternatively, one can approximate the projected 5-year risk of IBC very well from Table 2. First one computes a relative risk for the counselee by multiplying four relative risk factors. Then one multiplies this relative risk by the appropriate age- and race-specific baseline 5-year risk (Table 2). For example, consider a nulliparous 42-year-old white woman who began menstruating at age 12 years, who has no affected first-degree relatives, and who has had one previous breast biopsy with specimens interpreted as benign and no evidence of atypical hyperplasia. From Table 2, her relative risk is $1.10 \times 1.70 \times 1.55 \times 0.93 = 2.70$, and her projected 5-year risk of IBC is $2.70 \times 0.450 = 1.2\%$. The computer program also yields 1.2% in this case. The algorithm in Table 2 is an approximation because, unlike the computer program, it does not account for competing causes of death; such competing risks usually produce small effects over 5-year periods, however.

2) Projecting In Situ Breast Cancer

Because the proportion of *in situ* cancers depends on the intensity of screening and because women who take tamoxifen

Table 1. Validation of the model for projecting invasive breast cancer (IBC) in the BCPT placebo arm: comparison of observed with expected events*

	No. of women	Obs	Obs/Exp ratio	95% CI
Age, y				
<50	2332	60	0.93	0.72–1.22
50–59	1807	43	1.13	0.83–1.55
>59	1830	52	1.05	0.80–1.41
Total	5969	155	1.03	0.88–1.21
Quintiles of projected 5-y risk of IBC				
0–1.93	1189	23	0.70	0.47–1.11
1.94–2.41	1187	34	0.62	0.44–0.89
2.42–3.10	1197	20	1.36	0.88–2.22
3.11–4.17	1198	29	1.22	0.85–1.82
>4.17	1198	49	1.21	0.92–1.64
Total	5969	155	1.03	0.88–1.21

*BCPT = Breast Cancer Prevention Trial; Obs = observed; Exp = expected; CI = confidence interval.

Table 2. Relative risks and baseline rates used to estimate the risk of invasive breast cancer in the next 5 years*

Risk factor category		Relative risk factor	Age, y	Baseline 5-y risk, %	
				Black	Not black
A. Age at menarche, y					
⩾14		1.00	20–24	0.014	0.012
12–13		1.10	25–29	0.050	0.049
<12		1.21	30–34	0.120	0.134
			35–39	0.224	0.278
B. No. of breast biopsies			40–44	0.310	0.450
Age at counseling, <50 y old			45–49	0.355	0.584
0		1.00	50–54	0.416	0.703
1		1.70	55–59	0.511	0.859
⩾2		2.88			
Age at counseling, ⩾50 y old			60–64	0.562	1.018
0		1.00	65–69	0.586	1.116
1		1.27	70–74	0.646	1.157
⩾2		1.62	75–79	0.713	1.140
C. Age at first live birth, y	No. of first-degree relatives with breast cancer		80–84	0.659	1.006
<20	0	1.00			
	1	1.00			
	⩾2	6.80			
20–24	0	1.24			
	1	2.68			
	⩾2	5.78			
25–29 or nulliparous	0	1.55			
	1	2.76			
	⩾2	4.91			
⩾30	0	1.93			
	1	2.83			
	⩾2	4.17			
D. Atypical hyperplasia					
No biopsies		1.00			
At least one biopsy and no atypical hyperplasia found in any biopsy specimen		0.93			
No atypical hyperplasia found and hyperplasia status unknown for at least one biopsy specimen		1.00			
Atypical hyperplasia found in at least one biopsy specimen		1.82			

*To compute overall relative risk, multiply four component relative risks from categories A, B, C, and D. For example, a 42-year-old white nulliparous woman who began menstruating at age 12 years, who has no affected first-degree relatives, and who has had one previous breast biopsy with specimens interpreted as benign and no evidence of atypical hyperplasia has an overall relative risk of $1.10 \times 1.70 \times 1.55 \times 0.93 = 2.70$. From the data on 5-year baseline risk, her projected 5-year risk of invasive breast cancer is $2.70 \times 0.450 = 1.2\%$.

are likely to be in a program of annual screening with mammography, we recommend estimating the ratio of incidence rates of *in situ* breast cancer to IBC from populations receiving annual screening, such as the placebo arm (excluding those with LCIS) of the BCPT. These incidence ratios were estimated from BCPT data as 0.53 and 0.31, respectively, for the age groups 49 years old or younger and 50 years old or older. We recommend projecting the 5-year risk for *in situ* breast cancer by multiplying a woman's projected 5-year risk of IBC by the ratio appropriate to her age.

3) Other Strong Risk Factors and Protective Factors

The model of Gail et al. *(4)* and its modification for the BCPT were based on women in the BCDDP with no history of breast cancer or evidence of IBC or DCIS on their initial screening evaluation. Women who have had a previous breast cancer have a risk of developing contralateral disease five times higher than that of the general population *(12).* Women with LCIS in the placebo arm of the BCPT had a 5-year risk of IBC of 6.47%, which is 3.9 times the risk of an average 60-year-old woman and about twice the risk of other participants on the placebo arm of the BCPT. Risks for women with DCIS are even higher (*see* section V, part A). Thus, women with a previous breast cancer and women with LCIS or DCIS are at high risk, even compared with the population of high-risk women who entered the BCPT. Women known to carry cancer-causing mutations of the genes BRCA1 or BRCA2 are thought to have a cumulative breast cancer risk to age 70 years in the range 37%–85% *(13–15).* Such women constitute only about 0.7% of the general U.S. population, however *(16,17),* although perhaps 2% of Ashkenazi Jewish women are carriers *(13).* Other rare inherited disorders, such as Cowden's syndrome *(18)* and the Li–Fraumeni syndrome *(19),* also carry high risks of breast cancer. A woman from rural Japan or China has only one fifth of the risk of a woman of the same age from the United States *(20).* Available risk models do not explicitly take these strong risk factors or protective factors into account. Thus, when using available models, a counselor should look for these factors and modify risk estimates accordingly.

4) Alternative Modeling Approaches and Areas of Research

Claus et al. *(21)* used data from the Cancer and Steroid Hormone (CASH) Study to develop a risk projection model for IBC and *in situ* breast cancer based solely on the counselee's age and on detailed family history, including the ages at onset in affected relatives. The theory underlying this model is that all familial

risk is conferred by a single autosomal dominant gene. This model nicely explains why the proportion of mutation carriers is higher in women with breast cancer incident at younger ages than at older ages. Claus et al. *(22)* have shown, however, that the full extent of familial aggregation cannot be explained by current autosomal dominant models.

There are several opportunities for improving projections of breast cancer risk. One approach is to find and use additional strong risk factors. A promising candidate is the percentage of dense tissue observed in a baseline mammogram. Indeed, studies based on data in the Canadian National Breast Screening Study *(23)* and in the BCDDP *(24)* indicate that this factor is an even stronger predictor than family history. It might be possible to make more efficient use of family history information by using it to estimate the probability that a woman is a carrier of a BRCA1 or BRCA2 mutation *(25)*. Direct measurements of cancer-causing gene mutations in BRCA1 or BRCA2 would have an important bearing on risk projections, but such abnormalities are rare, even among women with breast cancer *(26)*.

B. Endometrial Cancer

We base predictions of endometrial cancer incidence rates on age- and race-specific SEER incidence rates from 1991 through 1995 (Table 3). To predict risk for women with a uterus, the SEER rates were divided by the estimated age-specific prevalence of having a uterus, obtained from Fig. 1 in Merrill and Feuer *(27)*. These prevalences were 0.88, 0.80, 0.72, 0.65, 0.64, 0.63, 0.62, 0.66, and 0.65, respectively, for the 5-year age intervals 35–39, . . . , 75–79. The same prevalence factors were used for white and black women, since we could find no data specific for black women.

In discussing the risk of endometrial cancer, counselors should be aware of risk factors that can increase or decrease risk compared with the composite average rates in Table 3. Important factors, such as long-term use of estrogens unopposed by progestins, are indicated in Table 4, but readers are urged to consult references *(28–31)* for details.

C. Stroke, Pulmonary Embolism, and Deep Vein Thrombosis

For white women and other nonblack women, the age-specific incidence rates (Table 3) for stroke, pulmonary embolism, and deep vein thrombosis are from studies of the predominantly white population of Rochester, MN. The data for strokes were taken from the period 1975–1984 in Fig. 2 of Broderick et al. *(32)*. Data for pulmonary embolism and deep vein thrombosis are from the period 1986 through 1990 in Table 1 of Silverstein et al. *(33)*. The age-adjusted stroke [International Classification of Diseases (ICD) code Nos. 430–438.9 *(34)*] mortality rate per 100 000 white women aged 35–84 years in Olmstead County, MN, was 69.8, compared with a U.S. rate of 92.2. Thus, stroke incidence rates for white women in Table 3 may underestimate U.S. incidence rates. These mortality data from 1979 through 1996 were obtained from http://wonder.cdc.gov and were adjusted to the 1990 U.S. white female population distribution. Similarly, the age-adjusted mortality rates for pulmonary embolism (ICD code Nos. 415–417.9) for white women aged 35–84 years were 8.1 for Minnesota, 10.2 for Olmstead County (where counts were too small to be reliable), and 8.1 for the United States.

Because few studies provide direct information on the incidence rates of stroke, pulmonary embolism, or deep vein thrombosis in black women, we estimated the incidence rates for black women by multiplying rates for white women by a black/white risk ratio. We estimated these ratios for strokes from stroke (ICD code Nos. 430–438.9) mortality ratios computed from Tables 1–27 in *Vital Statistics of the United States, 1992 (35)*. These ratios were 3.4, 2.8, 2.9, 2.3, and 1.2, respectively, for age groups less than 40 years, 40–49 years, 50–59 years, 60–69 years, and 70 years or older. Rates were age-adjusted within age groups to the 1990 U.S. populations for whites and blacks before these ratios were computed. The mortality ratios for pulmonary circulatory failure (ICD code Nos. 415–417.9), which is caused mainly by pulmonary emboli, were used for pulmonary embolism and deep vein thrombosis. These ratios were 2.9, 3.1, 3.0, 2.3, and 1.6 for the previous age groups, respectively.

Table 3. Incidence rates and total mortality rates per 1000 woman-years by race

	Rates for white women of ages					Rates for black women of ages				
Type of event	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y
Hip fracture*	0.038	0.038	1.016	2.416	7.437	0.032	0.032	0.548	0.921	2.834
Endometrial cancer†	0.020	0.210	0.814	1.442	1.632	0.010	0.083	0.353	0.888	0.881
Stroke‡	0.080	0.450	1.100	3.250	7.500	0.270	1.260	3.190	7.480	9.000
Pulmonary embolism§	0.070	0.150	0.500	0.880	1.930	0.200	0.460	1.500	2.020	3.090
Deep vein thrombosis§	0.430	0.490	0.550	0.980	1.610	1.250	1.520	1.650	2.250	2.580
Colles' fractures*	0.570	0.570	0.974	1.354	1.378	0.485	0.485	0.524	0.516	0.525
Spine fractures*	0.121	0.121	1.840	3.731	7.753	0.103	0.103	0.992	1.422	2.954
Cataracts‖	5.155	5.155	15.913	52.183	98.485	5.155	5.155	15.913	52.183	98.485
Total mortality¶	0.950	1.852	5.084	12.664	30.477	2.581	4.224	9.657	20.898	39.812

*Rates for white women were taken from *(45)*. Rate for Colles' fracture were assumed to represent 23% of all distal forearm fractures, as was found in the Breast Cancer Prevention Trial (BCPT). Rates for black women were obtained by multiplying the white rates by the white-to-black rate ratios for hip fracture in *(46)*. These ratios were 0.855, 0.539, and 0.381, respectively, for the age groups <50 years, 50–59 years, and >59 years.

†1991–1995 Surveillance, Epidemiology, and End Results rates adjusted for the prevalence of intact uteri (*see* section II, part B).

‡Rates for white women were taken from *(32)*. Rates for black women were obtained by multiplying the white rates by the black-to-white stroke mortality rate ratios for the United States in 1992. The ratios were 3.4, 2.8, 2.9, 2.3, and 1.2 for the respective age groups 35–39 years, . . . , 70–79 years.

§Rates for white women were taken from *(33)*. Rates for black women were obtained by multiplying the white rates by the black-to-white pulmonary circulatory failure mortality rate ratios for the United States in 1992. These ratios were 2.9, 3.1, 3.0, 2.3, and 1.6 for the respective age groups.

‖Rates observed in the BCPT placebo population.

¶Rates for the United States in 1990.

Table 4. Selected factors that modify risks of health outcomes in Table 3

Outcome	Factors	Effect on risk (relative risk)
Endometrial cancer	Unopposed estrogen replacement >10 y	Increased (5–10)
	Nulliparity; obesity; menopause after age 55 y	Increased (2)
	Diabetes; hypertension	Increase possibly related to obesity
	Estrogen with progestins	Little risk
	Oral contraceptives	Protective (0.5)
	Current smoking	Protective (0.5)
Stroke	Transient ischemic attack	Increased, especially in older women (5–30)
	Mitral valve disease; atrial fibrillation	Increased (2.5)
	Smoking; ischemic heart disease; diabetes; hypertension	Increased (2)
	Oral contraceptives; pregnancy; systemic lupus erythematosis	Increased
Pulmonary embolism or deep vein thrombosis	Trauma/surgery; immobility; pregnancy; smoking; obesity; oral contraceptives	Increased

Several studies confirm higher stroke incidence rates in black women than in white women. Rosamond et al. *(36)* presented data from the Atherosclerosis Risk in Communities (ARIC) cohort of 15 792 individuals aged 45–64 years from Jackson (MS), Forsyth County (NC), Washington County (MD), and Minneapolis (MN). The black/white stroke incidence ratios were 2.8 (95% CI = 1.4–5.5) for men and women under age 55 years and 2.2 (95% CI = 1.7–3.0) for older men and women. The overall stroke incidence ratios were the same in men and women, 2.66. Unpublished combined data from ARIC and from the Cardiovascular Health Study (CHS), which included 5873 men and women over age 64 years from Allegheny County (PA), Forsyth County (NC), Sacramento County (CA), and Washington County (MD) *(37,38)*, yielded a black/white incidence ratio for women aged 65–74 years of 2.4 (95% CI = 1.5–3.9). A study of stroke incidence in upper Manhattan (NY) *(39)* yielded black/white ratios of 3.0 for women of ages 40–59 years and 2.4 for women of ages 60–79 years. All of these data support the use of the stroke mortality ratios used in Table 3.

It is not surprising that black women in the general population have higher stroke rates than white women because they have a higher prevalence of risk factors such as hypertension *(38)*. Black/white stroke incidence ratios may be smaller in healthier populations, such as women who volunteer for prevention trials like the BCPT or the Women's Health Initiative (WHI) *(40)*. It is noteworthy, however, that, even after adjustment for age, gender, hypertension, diabetes, location, education, smoking, and coronary heart disease *(36)*, the black/white incidence ratio in ARIC was 1.4 (95% CI = 1.0–1.8).

The rates for stroke and pulmonary embolism in Table 3 overestimate the rates found in the placebo arm of the BCPT, possibly because healthy women tended to volunteer. Calculating the expected numbers of events from rates in Table 3, we found observed-to-expected ratios of 24/46.1 = 0.52, 6/14.3 = 0.42, and 22/18.5 = 1.19 for stroke, pulmonary embolism, and deep vein thrombosis, respectively. Combining stroke and pulmonary embolism, we found an observed-to-expected ratio of 30/60.2 = 0.50. In supplemental analyses to evaluate the sensitivity of our methods and to advise women who might volunteer for prevention trials, we multiplied the stroke and pulmonary embolism rates for white women in Table 3 by 0.50.

Table 4 lists factors other than age and race that increase the risk of stroke, pulmonary embolism, and deep vein thrombosis. *See* references *(41–43)* for details.

Pulmonary embolism and deep vein thrombosis can be considered together as venous thromboembolism because they frequently occur simultaneously and have the same risk factors *(43,44)*. These references provide details on the risk factors shown in Table 4.

D. Fractures

Estimated rates of fractures for white women (Table 3) of the proximal femur (hip), vertebra (spine), and distal forearm were obtained from studies in Rochester (MN) [*see* Table 1 in reference *(45)*]. Rates for Colles' fracture (Table 3) were obtained by multiplying rates for distal forearm fractures by 0.23, which was the fraction of distal forearm fractures classified as Colles' fractures in the BCPT. Silverman and Madison *(46)* calculated hip fracture incidence rates for non-Hispanic white women, Hispanic women, black women, and Asian women from hospital discharge data in California. The black/white ratios of incidence rates were 0.855, 0.539, and 0.381 for age groups less than 50 years, 50–59 years, and 60 years or more, respectively. We obtained rates for black women in Table 3 by multiplying rates for white women by these ratios. Compared with white women, Hispanic and Asian women had ratios 0.419, 0.240, and 0.334 and 0.435, 0.266, and 0.546, respectively, for these age groups *(46)*. Jacobsen et al. *(47)* reported rates of hip fractures in black and white women over age 64 years not very different from those in Table 3. Baron et al. *(48)* also reported similar rates of hip fractures to those in Table 3 in a 5% sample of the U.S. Medicare population aged 65–89 years, both for white and for black women.

In addition to age and race, other factors influence the risk of fractures in women. Women who have lost 20% of their weight since age 25 years have a 67% increase in hip fracture risk, adjusted for age and other factors [Table 2 in Cummings et al. *(49)*]. A number of other factors contribute to increased risk, including a history of maternal hip fracture, previous hyperthyroidism, current consumption of long-acting benzodiazapines, anticonvulsants or caffeine, lack of exercise (walking), inability to rise from a chair, previous fracture, and decreased bone density. Cummings et al. show how risk increases with decreasing bone density and with the number of other such risk factors.

E. Cataracts

Baseline estimates of cataract incidence (Table 3) were calculated from data in the placebo arm of the BCPT because this cohort of women reflects current ophthalmologic practice and is

the largest cohort with reports on cataracts in women. Cataract incidence was based on self-reports of cataract diagnoses. Unfortunately, the BCPT yielded little data on cataracts for black women, and we are unaware of other data on cataract incidence in black women. Data on race as a risk factor for lens opacity are inconsistent *(50).* Therefore, we used the same rates for black as for white women in Table 3. The rates in Table 3 are intermediate between the higher rates in studies in which cataracts are diagnosed solely on the basis of changes detected by slit-lamp examinations, without any requirement for a decrease in visual acuity *(51–53)* and the lower rates in studies that require, in addition to evidence of lens opacity, a decrease in visual acuity below 20/30 *(54,55).*

Certain medical conditions and medications, such as diabetes, oral steroids, and medicines for gout, are associated with a modestly increased risk of lens opacities, as are current smoking and low educational attainment *(50,56).* Current users of vitamin supplements have a reduced risk of lens opacities *(56).* Hodge et al. *(57)* reviewed studies of these and other risk factors.

III. Effects of Tamoxifen

Fisher et al. *(1)* described the effects of tamoxifen in the BCPT. Overall relative risks (tamoxifen to placebo) were 0.51 for IBC and 0.50 for *in situ* breast cancer (Table 5). There was no statistically significant evidence of heterogeneity of relative risks of invasive cancer across groups defined by age, number of affected first-degree relatives, projected 5-year risk of IBC, or LCIS status. We therefore assume that the relative risk reductions from tamoxifen for IBC and for *in situ* breast cancer are uniform across all subgroups. The preventive benefit of tamoxifen appeared to be greater in women with atypical hyperplasia, but the numbers of events were small among such women, and this subgroup was only one of five examined *(1).*

BCPT investigators *(1)* identified eight non-breast cancer conditions whose rates were affected by tamoxifen (Table 5). We have grouped all of the outcomes into the categories "life-threatening events," "severe events," and "other events" and labeled the individual conditions with numbers 1, 2, . . . 10 (Table 5). Because there was no statistically significant evidence of heterogeneity of relative risks across age groups for the non-breast cancer outcomes in Table 5, we used overall relative risks for each of the non-breast cancer outcomes except for endometrial cancer, for which it can be argued that menopausal status may influence the effect of tamoxifen. We, therefore, used the relative risk 4.01 found for women older than age 49 years for that age group. Even though there was no statistically significant evidence of increased risk with tamoxifen for women under age 50 years (relative risk = 1.21), the numbers were small; therefore, we used the overall relative risk, 2.53, for women under age 50 years. Data from other NSABP trials support this choice (*see* section VIII).

There is substantial uncertainty about the magnitude of the effects of tamoxifen for some of the outcomes, indicated by the 95% CIs in Table 5. The relative risks in Table 5 are based only on BCPT data. These relative risks are quite consistent, however, with the relative risks associated with adjuvant tamoxifen therapy in several analyses of the risk of contralateral breast cancer among women with resected breast cancer *(58)* and with the summary relative risk, obtained by a meta-analysis, of 0.53 for recurrent cancer or contralateral primary cancer among women on adjuvant tamoxifen therapy for 5 years *(59).* European studies with 41 women who developed breast cancers *(3)* and with 70 women who developed breast cancers *(2)* did not demonstrate a beneficial preventive effect of tamoxifen. These trials may be sufficiently different from the BCPT in design and execution that it is not reasonable to combine their data with those of the BCPT *(1).* Nonetheless, we can obtain a combined estimate of relative risk by taking the ratio of the number of breast cancers in the tamoxifen arms of the three studies to the number of breast cancers in the placebo groups. That ratio is (89 + 35 + 19 + 34)/(175 + 69 + 22 + 36) = 0.59 (95% CI = 0.49–0.71). Methods of combining results that account for possible differences in follow-up time cannot be used with the data presented in the European studies. Other methods that allow for heterogeneity of treatment effects across the three studies would place greater weight on the smaller studies *(60).* In section VIII, we discuss the impact of using the relative risk estimate 0.59 instead of the relative risks in Table 5.

These effects of tamoxifen were found even though many

Table 5. Numbers of events, incidence rates per 1000 woman-years, and relative risks in the Breast Cancer Prevention Trial

Type of event	No. of events		Average annual incidence rate per 1000		Relative risk	95% CI*
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Life-threatening events						
1) Invasive breast cancer	175	89	6.76	3.43	0.51	0.39–0.66
2) Hip fracture	22	12	0.84	0.46	0.55	0.25–1.15
3) Endometrial cancer						
All women	15	36	0.91	2.30	2.53	1.35–4.97
Women age ⩾50 y at entry	7	27	0.76	3.05	4.01	1.70–10.90
4) Stroke	24	38	0.92	1.45	1.59	0.93–2.77
5) Pulmonary embolism	6	18	0.23	0.69	3.01	1.15–9.27
Severe events						
6) *In situ* breast cancer	69	35	2.68	1.35	0.50	0.33–0.77
7) Deep vein thrombosis	22	35	0.84	1.34	1.60	0.91–2.86
Other events						
8) Colles' fracture	23	14	0.88	0.54	0.61	0.29–1.23
9) Spine fracture	31	23	1.18	0.88	0.74	0.41–1.32
10) Cataracts	507	574	21.72	24.82	1.14	1.01–1.29

*CI = confidence interval.

women discontinued its use during the course of these studies. In the BCPT, 23.7% discontinued treatment with tamoxifen for reasons not specified in the protocol, compared with 19.7% in the placebo group *(1)*, and 40% of women in the study by Powles et al. *(2)* stopped taking tamoxifen prematurely. It is not known whether the preventive effects of tamoxifen would have been greater had compliance been better.

IV. Risk/Benefit Comparisons for Women Eligible for BCPT

A. Statistical Methods

Relative risks, such as those in Table 5, do not convey the actual chance ("absolute risk") that tamoxifen will prevent or cause a woman to develop an adverse health outcome. We have, therefore, developed several additional tables to assist in weighing the risks and benefits from prophylactic tamoxifen use.

One approach is to describe fully the expected numbers of various adverse outcomes in a population of 10 000 untreated women followed for 5 years (Tables 6 and 7) and the corresponding numbers of events expected to be prevented (or caused) by tamoxifen (Tables 6 and 8). This full description allows a woman who is mainly concerned about particular outcomes, such as breast cancer or endometrial cancer, to focus on those absolute risks and the effects of tamoxifen on them.

To compute the number of invasive breast cancers expected in a population of 10 000 women with a given risk profile over a 5-year period, we multiplied the projected 5-year risk of IBC (in percent) from the breast cancer risk program (*see* section II, part A.1) by 100 (Table 6). The corresponding expected number of *in situ* lesions was obtained by multiplying this number by 0.53 for women under 50 years of age and by 0.31 for women older than age 49 years (*see* section II, part A.2; *see also* Table 6).

To compute the expected number of non-breast cancer events $N_{x,p}$ of type x ($x = 2, 3, 4, 5, 7, 8, 9, 10$ as defined in Table 5) in untreated women (Table 7), we assumed that the cause-specific hazard rates, I_x, and the mortality rates, M_x, from causes other than cause x are constant over the 5-year period. It follows that

$$N_{x,p} = 10\,000\{I_x/(I_x + M_x)\}[1 - \exp\{-5(I_x + M_x)\}]. \quad [1]$$

We used 1990 U.S. mortality rates derived from reference *(61)*. For non-breast cancer conditions, the rates I_x are obtained by dividing entries in Table 3 by 1000.

Expected events for a treated population, $N_{x,t}$, are obtained in the same way, except R_xI_x replaces I_x in equation 1, where R_x is the relative risk in Table 5. To obtain I_x for this calculation for IBC or *in situ* lesions, we solved equation 1 with known values of M_x and with $N_{x,p}$ obtained as described above from the risk program. The entries in Tables 6 and 8 representing the numbers of events prevented by (positive number) or caused by (negative number) tamoxifen are simply the differences $N_x = N_{x,p} - N_{x,t}$ rounded to the nearest integer.

To summarize the risks and benefits of tamoxifen in a single number, however, it is necessary to define indices that assign weights to the various events. A summary index based on the severity categories in Table 5 can be calculated from

$$I(W_1, W_2, W_3) = W_1\sum_{x=1}^{5} N_x + W_2\sum_{x=6}^{7} N_x + W_3\sum_{x=8}^{10} N_x, \quad [2]$$

where weights W_1, W_2, and W_3 are chosen to put varying emphasis on life-threatening, severe, and other events, respectively. We rounded indices to the nearest integer. We rely principally on the index $I(1, 0.5, 0)$ that puts twice as much weight on life-threatening events as on severe events and that ignores other events altogether. We also investigated the robustness of our conclusions to the use of other indices, i.e., $I(1, 1, 1)$, $I(1, 1, 0)$, and $I(1, 0.5, 0.25)$.

Table 6. Numbers of invasive ($N_{1,p}$) and *in situ* breast cancer cases ($N_{6,p}$) expected in 5 years among 10 000 untreated women and numbers of invasive (N_1) and *in situ* breast cancer cases (N_6) prevented by level of 5-year projected risk of invasive breast cancer (IBC)

	No. expected in 10 000 untreated women			No. prevented in 10 000 treated women		
		In situ breast cancer, $N_{6,p}$*			*In situ* breast cancer, N_6	
5-y projected risk of IBC, %	IBC, $N_{1,p}$	Age ≤49 y	Age ≥50 y	IBC, N_1†	Age ≤49 y	Age ≥50 y†
1.5	150	80	47	73	40	23
2.0	200	106	62	97	53	31
2.5	250	133	78	122	66	39
3.0	300	159	93	146	79	46
3.5	350	186	109	170	92	54
4.0	400	212	124	194	105	62
4.5	450	239	140	218	119	70‡
5.0	500	265	155	242	132	77
5.5	550	292	171	266§	145	85
6.0	600	318	186	289	158	93
6.5	650	345	202	313	172	100
7.0	700	371	217	337‖	184	108

*Assumes an *in situ*-to-invasive ratio of 0.53 for age ≤49 years and 0.31 for age ≥50 years.
†Value for all women unless otherwise noted.
‡Value is 69 for 60- to 69-year-old white women and for 70- to 79-year-old white and black women.
§Value is 265 for 60- to 69-year-old black women and for 70- to 79-year-old white and black women.
‖Value is 336 for 60- to 69-year-old black women and for 70- to 79-year-old white and black women.

Table 7. Numbers of non-breast cancer events expected in 5 years among 10 000 untreated women

Type of event	Age groups for white women					Age groups for black women				
	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y
Life-threatening events										
$N_{2,p}$: hip fracture	2	2	50	116	339	2	2	27	44	128
$N_{3,p}$: endometrial cancer	1	10	40	70	75	0	4	17	42	40
(without uterus)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
$N_{4,p}$: stroke	4	22	54	156	342	13	62	154	349	399
$N_{5,p}$: pulmonary embolism	3	7	25	43	89	10	23	73	95	139
Severe events										
$N_{7,p}$: deep vein thrombosis	21	24	27	47	74	62	75	80	106	116
Other events										
$N_{8,p}$: Colles' fracture	28	28	48	65	64	24	24	26	24	24
$N_{9,p}$: spine fracture	6	6	90	179	353	5	5	48	67	160
$N_{10,p}$: cataracts	254	253	755	2228	3629	253	252	747	2186	3555

Table 8. Numbers of non-breast cancer events prevented (positive number) or caused (negative number) in 5 years among 10 000 women treated with tamoxifen

Type of event	Age groups for white women					Age groups for black women				
	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y
Life-threatening events										
N_2: hip fracture	1	1	22	52	151	1	1	12	20	57
N_3: endometrial cancer	−2	−16	−120	−206	−223	−1	−6	−52	−126	−119
(without uterus)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
N_4: stroke	−2	−13	−32	−91	−196	−8	−36	−90	−200	−228
N_5: pulmonary embolism	−7	−15	−49	−85	−177	−20	−46	−145	−189	−273
Severe events										
N_7: deep vein thrombosis	−13	−15	−16	−28	−44	−37	−45	−48	−63	−69
Other events										
N_8: Colles' fracture	11	11	19	25	25	9	9	10	10	9
N_9: spine fracture	2	2	23	46	90	1	1	13	17	62
N_{10}: cataracts	−35	−35	−101	−269	−384	−35	−35	−100	−264	−377

In addition to tabulating $I(1, 0.5, 0)$ for various types of women, we analyzed the random variability of the data to estimate the probability that the index is positive. To compute these probabilities, we assumed that the only random elements in $N_{x,p}$, $N_{x,t}$, and equation 2 are the relative risks in Table 5 that affect the calculation of $N_{x,t}$ from equation 1 with R_xI_x in place of I_x. Let U and V be the observed numbers of a particular adverse event, x, in the tamoxifen and placebo arms, respectively, of the BCPT. We assume U and V are independent Poisson variates with means λ_U and λ_V and that λ_U and λ_V have independent noninformative exponential prior distributions with means tending to infinity. Then the posterior distributions of $2\lambda_U$ and $2\lambda_V$ are independent chi-squared distributions with $2(U + 1)$ and $2(V + 1)$ degrees of freedom, respectively. It follows that R_x is distributed as $\{(U + 1)/(V + 1)\}\{P_V/P_U\}F_{2(U+1),2(V+1)}$, where P_U and P_V are the respective person-years of exposure in the tamoxifen and placebo groups. Thus, to obtain an estimate of the probability that $I(1, 0.5, 0)$ exceeds zero, we resampled R_x independently for each x and recalculated $I(1, 0.5, 0)$. We repeated this process 1 000 000 times and estimated the desired probability (with precision ±0.001) as the proportion of samples in which $I(1, 0.5, 0)$ exceeded zero. Using a parametric bootstrap with resampled Poisson counts instead of the Bayesian approach above, we obtained similar results.

B. Expected Events in the Absence of Tamoxifen and Numbers of Events Prevented or Caused by Tamoxifen among 10 000 Women Over a 5-Year Period

The numbers of IBCs ($N_{1,p}$) and *in situ* breast cancers ($N_{6,p}$) expected to develop in a population of 10 000 untreated women over a 5-year period depends directly on the projected 5-year risk of IBC (Table 6). For a given projected 5-year risk of IBC, the expectations for *in situ* breast cancer are 0.53/0.31 = 1.7 times higher in women under 50 years of age compared with those 50 years old or older (*see* section II).

The numbers of expected non-breast cancer events increase with age and vary by race (Table 7). The variations of the frequency of events reflect the variation in the expected rates by age and race. Cataracts are by far the most common event. Hip and spine fractures are rare, and the occurrence of a stroke is infrequent among women under age 50 years, but these conditions are relatively frequent among those 70 years old or older. Several differences between white and black women are important to note. In those over 50 years of age, fractures are about two to three times more common among white women. Depending on age, the frequency of endometrial cancer is 1.5–2.5 times higher among white women. Stroke, pulmonary embolism, and deep vein thrombosis are two to three times higher among black women in all age groups.

The numbers of cases of IBCs (N_1) and *in situ* breast cancers (N_6) expected to be prevented by tamoxifen among 10 000 women over a 5-year period are shown in Table 6. Because tamoxifen reduces the incidence of breast cancer by about one half, the numbers of breast cancers expected to be prevented are nearly proportional to the projected 5-year risk of IBC.

Table 8 displays the expected numbers of non-breast cancer outcomes prevented (positive number) or caused (negative number) by tamoxifen in such a population. The patterns in Table 8 reflect variations in background rates (Table 7) and the relative risks associated with tamoxifen therapy (Table 5). Among women 50 years old or older, tamoxifen reduces the expected numbers of fractures substantially. This benefit is counterbalanced by substantial increases in the risks of stroke, pulmonary embolism, and deep vein thrombosis in women 60 years old or older, especially among black women. The risk of tamoxifen-induced endometrial cancer is also appreciable in women 50 years old or older with a uterus and is about twofold higher in white women than in black women. Tamoxifen causes very few adverse events among black or white women under age 50 years and has the potential to prevent IBCs and *in situ* breast cancers among high-risk women in this age range.

C. Examples of Assessing Risks and Benefits From Tables 6–9

We illustrate how black and white women in the age groups 40–49 years or 50–59 years and with projected 5-year risks of IBC of 2.0%, 4.0%, or 6.0% can assess the net benefit or risk from tamoxifen (Table 9). Table 9 was constructed by abstracting appropriate elements from Tables 6 and 8.

First consider a 45-year-old white woman with a projected 5-year risk of IBC of 4%. Such a woman would have several strong risk factors for breast cancer (*see* section II). She can expect a net reduction of absolute risk of 151 life-threatening events per 10 000 women in 5 years or a reduction in her personal risk of 1.51% in 5 years (Table 9). This reduction in the risk of life-threatening events is large, compared with the general 5-year probability of death, 0.92%, in this age range. The overall 5-year mortality can be approximated by multiplying the rates in Table 3 by 0.005 and compared with the background risk of IBC (Table 6) and non-breast cancer life-threatening events (Table 7). Such a woman can also anticipate a reduction of 90 severe events (0.90%) and a slight increase in the risk of other events (22 events or 0.22%). If she is concerned only with life-threatening events, she might use the index $I(1, 0, 0) = 151$. If she has no uterus, $I(1, 0, 0) = 151 + 16 = 167$. If she weighs life-threatening events twice as heavily as severe events and ignores other events, she could use the index $I(1, 0.5, 0) = 196$ (Table 9). This index rises to 212 if the woman has no uterus. If the woman were 55 years old instead of 45 years old, her indices would be less favorable. In particular, $I(1, 0, 0) = 15$ and $I(1, 0.5, 0) = 38$, primarily because of increasing risk of endometrial cancer. If the 55-year-old woman has no uterus, $I(1, 0, 0) = 15 + 120 = 135$, and $I(1, 0.5, 0) = 158$.

A 55-year-old black woman with a projected 5-year risk of IBC of 4% would expect a net adverse effect from tamoxifen among 10 000 such women of –81 life-threatening events in 5 years (0.81% increase in absolute risk), primarily from increased risk of stroke and pulmonary embolism. The index $I(1, 0.5, 0) = -74$ if she has a uterus and −22 otherwise. The data therefore suggest that such a woman is unlikely to benefit from using tamoxifen. It should be remembered, however, that the data on baseline rates and effects of tamoxifen are much less well established for black women than for white women (*see* sections II and III); therefore these conclusions are subject to greater uncertainty.

Table 9. Examples of the net benefit/risk index for a group of 10 000 women treated with tamoxifen who have a 5-year projected risk of invasive breast cancer of 2.0%, 4.0%, or 6.0% and who are in the age range 40–59 years with or without a uterus*

		White women						Black women					
		2.0% risk		4.0% risk		6.0% risk		2.0% risk		4.0% risk		6.0% risk	
Severity of event	Type of event	Age 40–49 y	Age 50–59 y	Age 40–49 y	Age 50–59 y	Age 40–49 y	Age 50–59 y	Age 40–49 y	Age 50–59 y	Age 40–49 y	Age 50–59 y	Age 40–49 y	Age 50–59 y
Life-threatening	N_1: invasive breast cancer	97	97	194	194	289	289	97	97	194	194	289	289
	N_2: hip fracture	1	22	1	22	1	22	1	12	1	12	1	12
	N_3: endometrial cancer	−16	−120	−16	−120	−16	−120	−6	−52	−6	−52	−6	−52
	N_4: stroke	−13	−32	−13	−32	−13	−32	−36	−90	−36	−90	−36	−90
	N_5: pulmonary embolism	−15	−49	−15	−49	−15	−49	−46	−145	−46	−145	−46	−145
		54	−82	151	15	246	110	10	−178	107	−81	202	14
Severe	N_6: *in situ* breast cancer	53	31	105	62	158	93	53	31	105	62	158	93
	N_7: deep vein thrombosis	−15	−16	−15	−16	−15	−16	−45	−48	−45	−48	−45	−48
		38	15	90	46	143	77	8	−17	60	14	113	45
Other	N_8: Colles' fracture	11	19	11	19	11	19	9	10	9	10	9	10
	N_9: spine fracture	2	23	2	23	2	23	1	13	1	13	1	13
	N_{10}: cataracts	−35	−101	−35	−101	−35	−101	−35	−100	−35	−100	−35	−100
		−22	−59	−22	−59	−22	−59	−25	−77	−25	−77	−25	−77
Net benefit/risk index $I(1, 0.5, 0)$ with uterus		73	−75	196	38	318	149	14	−187	137	−74	259	37
Net benefit/risk index $I(1, 0.5, 0)$ without uterus		89	46	212	158	334	269	20	−135	143	−22	265	89

**See* section IV, part A, of the text for explanation of net benefit/risk index.

Some generalizations can be made based on $I(1, 0.5, 0)$ in Table 9. First, the net index increases with increasing projected 5-year risk of IBC. Second, within any particular level of projected 5-year risk of IBC, the net index decreases with increasing age as the result of increases in the risk of adverse effects of tamoxifen treatment. Third, the elimination of the risk of endometrial cancer among women 50 years old or older (as in those who have had a hysterectomy) substantially improves the net index. This is particularly notable among white women with a low risk of breast cancer, for whom the elimination of endometrial cancer risk improves the index from a negative value to a positive value. Fourth, because the risks of events, such as stroke, pulmonary embolism, and deep vein thrombosis, are two to three times higher in black women, the net indices for black women are lower than those for white women.

D. Some General Recommendations Based on the Index $I(1, 0.5, 0)$ in Tables 10 and 11

These points can be studied further by examining the patterns of values of $I(1, 0.5, 0)$ for women with (Table 10) and without (Table 11) a uterus. In addition to the value of $I(1, 0.5, 0)$, both tables display an asterisk when the probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account (*see* section IV, part A), is 0.60–0.89 and two asterisks when the probability equals or exceeds 0.90. Thus, two asterisks indicate "strong evidence" that tamoxifen is beneficial based on weights $W_1 = 1$, $W_2 = 0.5$, and $W_3 = 0$, and one asterisk indicates "moderate evidence" of a net benefit.

The patterns of values of $I(1, 0.5, 0)$ in Tables 10 and 11 suggest certain classes of women who are likely to benefit from prophylactic use of tamoxifen. The largest positive entry in Table 10 is 413 for a white woman aged 35–39 years with a projected 5-year risk of IBC of 7.0%. If we think of each severe event as equivalent to half of a life-threatening event, this number translates to a reduction in the absolute risk of a life-threatening event of 4.13% over a 5-year period, which is large, especially in comparison with the 5-year mortality rate of 0.47%. Many other positive entries in Table 10 are smaller, even though there is strong evidence, indicated by two asterisks, that the net benefit is positive. For example, if a 45-year-old white woman with a uterus had a projected 5-year risk of IBC of 1.5%, she would have an expected reduction in absolute 5-year risk of only 0.43%. Thus, it is important to look at the magnitude of the effects in Tables 10 and 11 as well as whether there is strong statistical evidence that the net effects are positive, as indicated by the asterisks.

Nonetheless, we can summarize the information in Tables 10 and 11 that identifies women for whom there is strong evidence (two asterisks) or moderate evidence (one asterisk) that $I(1, 0.5, 0)$ exceeds zero (Fig. 1). Among white women with a projected 5-year risk of IBC between 1.5% and 7.0%, there is strong evidence of a net tamoxifen benefit for all those under age 50 years. For those with a uterus, strong evidence of benefit is also found for women aged 50–59 years with a projected 5-year risk of IBC greater than or equal to 6.0%, and moderate evidence of net benefit is found for those with a projected 5-year risk of IBC in the range of 4.0%–5.9%. For white women without a uterus, strong evidence of benefit is also found in some high-risk women aged 60–69 years (*see* Fig. 1).

For black women, strong evidence of a net tamoxifen benefit is confined to younger age groups, where the risks from stroke, pulmonary embolism, and deep vein thrombosis are smaller (Fig. 1).

Unreported data reveal very similar patterns to those in Tables 10 and 11 and Fig. 1 for $I(1, 1, 1)$, $I(1, 0, 0)$, and $I(1, 0.5, 0.25)$. Thus, these conclusions are fairly insensitive to the precise weights used, provided the weights emphasize life-threatening and severe events.

E. Volunteers for Prevention Trials

Women in the placebo arm of the BCPT had lower mortality rates (71 deaths observed compared with 188 expected from the mortality rates in Table 3) and lower rates of stroke and pulmonary embolism than the general population (*see* section II, part C). Women who participate in prevention trials such as the BCPT and the WHI tend to be "healthy volunteers." To assess the sensitivity of the results in Tables 10 and 11 to lower rates of stroke and pulmonary embolism and to offer information to women who are considering participating in prevention trials and to other comparably healthy women, we multiplied the rates of stroke and pulmonary embolism in Table 3 for white women by the observed-to-expected ratio for stroke and pulmonary embolism in the placebo arm of the BCPT, 0.50 (*see* section II, part C). These reduced rates of stroke and pulmonary embolism were

Table 10. Net benefit/risk indices for tamoxifen treatment by level of 5-year projected risk of invasive breast cancer (IBC), age group, and race for women with a uterus (*see* section IV of the text for explanation of net benefit/risk index)

5-y projected risk of IBC, %	Age groups for white women					Age groups for black women				
	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y
1.5	77**	43**	−103	−260	−383	47**	−17	−215	−442	−513
2.0	107**	73**	−75	−232	−355	77**	14	−187	−414	−485
2.5	139**	105**	−46	−203	−326	109**	46*	−158	−385	−456
3.0	169**	135**	−18	−175	−298	139**	76*	−130	−358	−429
3.5	200**	166**	10	−147	−270	170**	107**	−102	−330	−401
4.0	230**	196**	38*	−119	−242	200**	137**	−74	−302	−373
4.5	261**	227**	66*	−92	−215	231**	168**	−46	−274	−345
5.0	292**	258**	94*	−64	−187	262**	199**	−19	−246	−317
5.5	322**	288**	122*	−36	−160	292**	229**	10	−219	−290
6.0	352**	318**	149**	−9	−132	322**	259**	37	−191	−262
6.5	383**	349**	176**	19	−104	353**	290**	64*	−164	−235
7.0	413**	379**	204**	47	−77	383**	320**	92*	−137	−208

*The probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account, is estimated to be in the range of 0.60–0.89.

**The probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account, is estimated to be in the range of 0.90–1.00.

Table 11. Net benefit/risk indices for tamoxifen treatment by level of 5-year projected risk of invasive breast cancer (IBC), age group, and race for women without a uterus (*see* section IV of the text for explanation of net benefit/risk index)

5-y projected risk of IBC, %	Age groups for white women					Age groups for black women				
	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y
1.5	79**	59**	18*	−54	−160	48**	−11	−163	−316	−394
2.0	109**	89**	46*	−26	−132	78**	20*	−135	−288	−366
2.5	141**	121**	75*	4	−103	110**	52*	−106	−259	−337
3.0	171**	151**	102**	31	−75	140**	82**	−78	−232	−310
3.5	202**	182**	130**	59*	−47	171**	113**	−50	−204	−282
4.0	232**	212**	158**	87*	−19	201**	143**	−22	−176	−254
4.5	263**	243**	186**	115*	9	232**	174**	6	−148	−226
5.0	294**	274**	214**	143*	37	263**	205**	34	−120	−189
5.5	324**	304**	242**	171**	64	293**	235**	62*	−93	−171
6.0	354**	334**	269**	198**	92*	323**	265**	89*	−65	−143
6.5	385**	365**	296**	225**	119*	354**	296**	116*	−38	−116
7.0	415**	395**	324**	253**	146*	384**	326**	144*	−11	−89

*The probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account, is estimated to be in the range of 0.60–0.89.
**The probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account, is estimated to be in the range of 0.90–1.00.

used to calculate the index $I(1, 0.5, 0)$ in Table 12 for white women with and without a uterus. It is seen that, compared with indices in Tables 10 and 11, the indices in Table 12 are larger, especially for older ages. For example, a 65-year-old white woman with a uterus and with a projected 5-year risk of IBC of 3% has an index equal to –175 in Table 10 and an index equal to –88 in Table 12. Thus, the risk/benefit trade-off is improved in "healthy volunteers."

Black women who participate in prevention trials such as the WHI and the BCPT are also likely to have lower rates of stroke and pulmonary embolism than in the general population (*see* section II, part C), and their indices may be more akin to those in Table 12 than to those in Tables 10 and 11. Table 12 could also be used in place of Tables 10 and 11 for women who have a risk factor profile that indicates they are at low risk for stroke and pulmonary embolism.

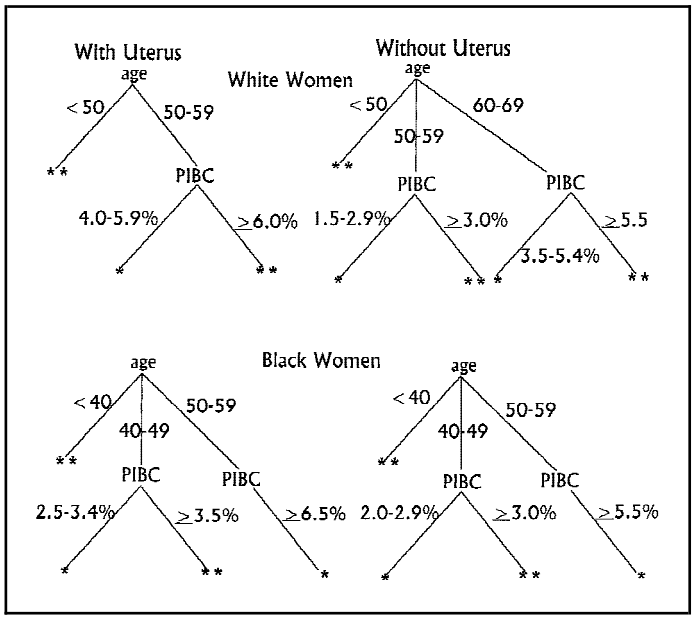

Fig. 1. Classification of the probability that $I(1, 0.5, 0)$ exceeds zero among women with a projected 5-year risk of invasive breast cancer (PIBC) of at least 1.5%. I = summary index; 1 = weight assigned to life-threatening events; 0.5 = weight assigned to severe events; 0 = weight assigned to other events. **One asterisk** indicates a probability of 0.60–0.89, providing moderate evidence of a net benefit with tamoxifen; **two asterisks** indicate a probability of 0.90–1.00, providing strong evidence that tamoxifen is beneficial. To assess the magnitude of the benefit, *see* Tables 10 and 11. Age is given in years. *See* text for additional details.

F. Lobular Carcinoma *In Situ*

Women with LCIS had a projected 5-year risk of IBC of 6.47% in the BCPT. We therefore recommend using the projected 5-year risk of IBC of 6.5% as the entry in Tables 6, 8, 10, and 11 and Fig. 1 for such women.

V. Applicability of Trial Results to High-Risk Women Not Included in the BCPT

Although the BCPT did not include the following classes of women, many such women are seeking advice on the possible use of tamoxifen. Realizing that direct data from clinical trials would be needed to establish the role of tamoxifen definitively, we nonetheless offer some informed opinions based on workshop discussion and other sources.

A. Ductal Carcinoma *In Situ*

Women with a history of DCIS may be candidates for primary prevention with tamoxifen because they are at high risk for invasive breast cancer. Women treated with lumpectomy alone in NSABP protocol B-17, which compared lumpectomy with lumpectomy plus radiation *(62)*, had a 5-year risk of IBC of 14.7%. IBC includes contralateral breast cancer. The risk of contralateral invasive breast cancer alone was 1.89%. The 5-year cumulative risk of IBC for women treated with lumpectomy and radiation was 6.9% in NSABP protocol B-17 *(62)* and 7.2% in protocol B-24, which studied lumpectomy and radiation with or without tamoxifen *(63)*. The corresponding 5-year cumulative risks of contralateral invasive cancer were 2.1% and 2.3%, respectively. Thus, the risk of contralateral disease alone in these studies is comparable to the 5-year risk of all IBCs, 3.3%, seen in the placebo arm of the BCPT, and the 5-year risk for all IBCs for women with DCIS is quite high compared with that for BCPT participants. Based on these high 5-year risks, even in women treated with lumpectomy and radiation, the data in

Table 12. Net benefit/risk indices for tamoxifen treatment for white women with background risks of stroke and pulmonary embolism reduced to levels found in the placebo arm of the Breast Cancer Prevention Trial, by level of projected 5-year risk of invasive breast cancer (IBC), age group, and status of uterus (*see* section IV of the text for explanation of net benefit/risk index)

5-y projected risk of IBC, %	Age groups for white women with a uterus					Age groups for white women without a uterus				
	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y	35–39 y	40–49 y	50–59 y	60–69 y	70–79 y
1.5	81**	57**	−63	−173	−199	83**	73**	58**	34*	25
2.0	111**	87**	−35	−145	−171	113**	103**	86**	62*	53*
2.5	143**	119**	−6	−116	−142	145**	135**	115**	91**	82*
3.0	173**	149**	22*	−88	−114	175**	165**	142**	118**	109*
3.5	204**	180**	50*	−60	−86	206**	196**	170**	146**	137*
4.0	234**	210**	78*	−32	−58	236**	226**	198**	174**	165*
4.5	265**	241**	106*	−5	−31	267**	257**	226**	202**	193*
5.0	296**	272**	134**	24	−3	298**	288**	254**	230**	221**
5.5	326**	302**	162**	52*	25	328**	318**	282**	258**	248**
6.0	356**	332**	189**	79*	53	358**	348**	309**	285**	276**
6.5	387**	363**	216**	106*	80*	389**	379**	336**	312**	303**
7.0	417**	393**	244**	134*	107*	419**	409**	364**	340**	330**

*The probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account, is estimated to be in the range of 0.60–0.89.

**The probability that $I(1, 0.5, 0)$ exceeds zero, taking random variation into account, is estimated to be in the range of 0.90–1.00.

Tables 8–12 and Fig. 1 suggest a potential benefit for some women with DCIS. Such women were excluded from BCPT because they were eligible for a competing protocol and not because it was thought that tamoxifen would be ineffective.

B. Recent Small, Invasive Breast Cancers

Women with a history of IBC have a risk of about 0.6% per year of developing a second, contralateral, primary breast tumor *(59).* This corresponds to 5-year risks of about 3%, which is near the risk of IBC of 3.3% for members of the BCPT placebo arm. Consensus opinion suggests that adjuvant therapy with tamoxifen is not indicated for women with invasive breast tumors less than 1 cm in size who have negative axillary lymph nodes *(59).* However, the consensus opinion was based on studies of tamoxifen as a treatment for primary cancer rather than as a preventive agent against a second new breast cancer. Because the risk of a contralateral, second invasive breast malignancy approaches 20% during the remaining years of life of a woman diagnosed with a first breast cancer at the age of 40 years and is similar to the risk for women in the BCPT, the use of tamoxifen for risk reduction may be a reasonable option, particularly for younger women. There are no data available from studies designed to examine this question, but a review of data from NSABP treatment trials and other trials showed that tamoxifen reduces the incidence of contralateral second primary breast cancers by roughly the same proportion as observed for primary breast malignancies in the BCPT *(58).* Thus, preventive use of tamoxifen for women with small, lymph node-negative invasive breast cancers may be justified in some cases where there is doubt about its use as adjuvant therapy.

It is not known whether some breast cancers arise without expressing estrogen receptors (ERs) at any point in their genesis or whether all invasive breast cancers pass through a developmental phase in which they produce ER protein. The data from the BCPT indicate that the breast cancers arising among women taking placebo were more likely to express ERs than were those arising in women taking tamoxifen. This suggests that tamoxifen suppressed those developing lesions that expressed ERs but had little or no effect on tumors that did not express ERs. An alternative explanation is that there are breast tumors that arise without expressing ERs at any time in their natural history. If the latter hypothesis is true and if subsequent breast cancers in women whose first cancer did not express ERs are also ER negative, tamoxifen would offer them little benefit. Alternatively, if all breast tumors pass through a phase of ER expression, then tamoxifen may offer benefit even to those women whose first primary breast cancer was ER negative. Although more basic and clinical research is necessary to resolve this question, a meta-analysis of the effects of tamoxifen *(59)* revealed that "the proportional reduction in contralateral breast cancer appeared to be about the same size in women with ER-poor tumours (29% [SD 15]) as in other women (30% [SD 6])."

C. Remote Diagnosis of Breast Cancer

Another group of women for whom there is no definitive answer about the use of tamoxifen for prevention are cancer-free women who were diagnosed with breast cancer 5 or more years previously ("remote diagnosis") and who were not treated with adjuvant tamoxifen. We abstracted data from several NSABP protocols *(64–67)* to estimate the subsequent risk of IBC in women who had survived disease free for 5 years following an initial IBC diagnosis and who had not received adjuvant tamoxifen. The subsequent 5-year cumulative risk of contralateral invasive breast cancer was 3.4%, which is close to the risk of 3.3% for IBC in the placebo arm of the BCPT, and the cumulative risk of all IBCs in such women was 14.4%. The decision to use tamoxifen for risk reduction in these patients must be informed by an assessment of the duration and quality of life remaining, the risks as well as potential benefits of tamoxifen, and the presence of competing morbidities that may weigh against the use of tamoxifen. For example, tamoxifen might be appropriate in a 50-year-old woman who is otherwise healthy, but it might be less suitable in a 68-year-old woman with a history of cataracts and deep vein thrombosis.

D. BRCA1/2 Mutation Carriers

Both prospective and retrospective genetic epidemiologic studies *(13–15)* have demonstrated that women who carry mutations in either the BRCA1 or BRCA2 genes are at very high risk of developing both breast and ovarian cancers. These

women would appear to be ideal candidates for the use of tamoxifen in the primary prevention of breast cancer, but no data are yet available that relate directly to such women. While the mechanisms by which tamoxifen might prevent breast cancer in BRCA1/2 mutation carriers are not fully understood, there is no reason to suppose *a priori* that tamoxifen would necessarily be less effective in mutation carriers, other than the observation that BRCA1 mutation carriers are more likely to develop ER-negative tumors *(68–72)*. Additional laboratory modeling of the effects of tamoxifen *in vitro* is necessary to address this question, as are prospective data from primary prevention trials that use tamoxifen in mutation carriers. Until these studies are completed, the use of tamoxifen in such women should be accompanied by disclosure beforehand that tamoxifen may not be effective.

VI. Clinical Monitoring of Women on Tamoxifen

Experience with appropriate clinical management and follow-up of women taking tamoxifen for primary prevention is limited to only a few studies *(1–3)* and principally to the BCPT. Surprisingly little published information is available from clinical trials that used tamoxifen to treat breast cancer. Endometrial hyperplasia (unpublished data from the BCPT) and endometrial cancer *(1)* were more frequent among women taking tamoxifen than among women taking placebo in the BCPT, but there was no statistically significant evidence *(1)* of an elevated risk of endometrial cancer with tamoxifen in women under age 50 years (relative risk = 1.21; 95% CI = 0.41–3.60). There is insufficient evidence for or against the use of transvaginal ultrasound or endometrial sampling for the early detection of endometrial cancer *(73)*, and the American College of Obstetrics and Gynecology *(74)* has issued the recommendation that women on tamoxifen should have annual gynecologic examinations with Pap tests and pelvic examinations. Any abnormal bleeding should be evaluated with appropriate diagnostic testing. Women should be counseled about the risk of benign and malignant conditions associated with tamoxifen. Screening procedures or diagnostic tests should be at the discretion of the treating physicians, and options should be discussed with women who are considering taking tamoxifen.

Routine screening with hematologic or chemical blood tests is not indicated because no hematologic or hepatic toxic effects attributable to tamoxifen were demonstrated in the BCPT or in clinical trials using tamoxifen as adjuvant therapy.

Because of the modest increase in the risk of cataracts (relative risk = 1.14) and cataract surgery among women on tamoxifen compared with women taking placebo, women taking tamoxifen should be questioned about symptoms of cataracts during follow-up and should discuss with their health care provider the value of periodic eye examinations.

VII. Counseling

Health care providers who counsel women about tamoxifen should strive to ensure that the patient makes a fully informed decision that incorporates her personal values and preferences. The counseling process should be interactive and sensitive to the woman's educational level and cultural background. Research suggests that women who were actively involved in decision-making about hormone replacement therapy were more satisfied with their decisions and more informed *(75)*. Because an individual's preferences and risk status can change substantially over time, it is also important that decisions about tamoxifen not be regarded by either patient or counselor as urgent or irreversible.

Any discussion of tamoxifen should occur within the context of a broader discussion of health promotion and breast cancer risk. The encounter should include a qualitative assessment of the patient's risk and, ideally, a quantitative assessment. The woman's perception of her own risk should be elicited so that it can be compared with an objective risk estimate. This discussion might include an evaluation of the psychologic factors that may affect a woman's perception of her risk, including her personal experience of breast cancer in family members, and her beliefs and fears concerning cancer etiology and treatment. Research indicates that, although the perceived risk of breast cancer can be highly inaccurate, it is associated with health behaviors, such as the use of mammography *(76)*. Therefore, counselors should strive to ensure that a woman understands her objective risk and its implications for making a decision about the use of tamoxifen.

At a minimum, a risk assessment encounter should include a clear description of the benefits and risks of taking tamoxifen for the individual woman, including a description of the side effects experienced by some of the BCPT study participants. Based on the counselee's age, race, and projected 5-year risk of IBC, one could refer to Fig. 1 to determine whether there is strong evidence for a net benefit of tamoxifen and to Table 10 or 11 to assess the magnitude of the benefit, expressed in terms of the index $I(1, 0.5, 0)$. The counselor should also take into account particular risk factors (*see* section II and Table 4) to see if the woman is subject to increased risk of tamoxifen-induced stroke or endometrial cancer, for example. Such factors would require a more detailed calculation of likely risks associated with tamoxifen by modifying Tables 6 and 8.

The woman should be shown a summary of the separate risks and benefits of tamoxifen, as illustrated in Table 13, to allow her to weigh various outcomes individually. Some women may reject tamoxifen because they fear a stroke or a pulmonary embolism, even though the net benefit index is positive. The summary data in Table 13 are based on age, race, presence or absence of a uterus, and projected 5-year risk of IBC. Table 13 exhibits for a 40-year-old white woman with a uterus and with a projected 5-year risk of IBC of 2% the numbers of severe and life-threatening events expected in a population of 10 000 women like the counselee in 5 years in the absence of tamoxifen, the number of such events expected to be prevented or caused by tamoxifen, a description of tamoxifen's effects on events that are not severe or life-threatening, and an estimate of $I(1, 0.5, 0)$. From data in a table such as Table 13 and from data in Tables 6 and 8, the woman and her counselor would have the information needed to calculate any summary index that they chose, based on the woman's particular health concerns and her preferred weights, and to compare the effects of tamoxifen with rates in the absence of tamoxifen. Some women with a negative $I(1, 0.5, 0)$ index may choose to take tamoxifen to reduce their breast cancer risk, and the counselor should be prepared to support such a decision if it represents an informed choice. Experience in the BCPT indicates that tools to communicate the risks and benefits of tamoxifen must be simple and short, and Fig. 1 and summaries such as Table 13 may therefore prove useful. The

Table 13. Example of a tool for data presentation for communicating the benefits and risks of tamoxifen treatment

Summary of benefits and risks associated with tamoxifen use based on results from the Breast Cancer Prevention Trial: This table gives the number of certain events that would be expected during the next 5 years among 10 000 untreated 40-year-old white women who have a uterus and who have a projected 5-year risk of invasive breast cancer of 2.0%, just like you. To help you understand the potential benefits and risks of treatment, these numbers can be compared with the number of expected cases that would be prevented or caused by 5 years of tamoxifen use.

Severity of event	Type of event	Expected No. of cases among 10 000 untreated women	Expected effect among 10 000 women who were treated with tamoxifen for 5 y
			Potential benefits
Life-threatening	Invasive breast cancer	200	97 cases may be prevented
	Hip fracture	2	1 case may be prevented
			Potential risks
	Endometrial cancer	10	16 more cases may be caused
	Stroke	22	13 more cases may be caused
	Pulmonary embolism	7	15 more cases may be caused
			Potential benefit
Severe	*In situ* breast cancer	106	53 cases may be prevented
			Potential risk
	Deep vein thrombosis	24	15 more cases may be caused
Others	Potential benefits: Tamoxifen may reduce the risk of a certain type of wrist fracture called Colles' fracture by about 39% and may also reduce the risk from fractures of the spine by about 26%.		
	Potential risk: Tamoxifen use may increase the occurrence of cataracts by about 14%.		
	Net No. of life-threatening events prevented = 54		
	Net No. of severe events prevented = 38		
	Net benefit/risk index based on number of life-threatening events prevented plus half the No. of severe events prevented = 73		

need for simplicity in communicating information on risks and benefits has been stressed elsewhere *(77).*

Written materials alone are likely to be insufficient, and the counselor may find that verbal explanations and comparisons to other risks may be needed to explain the risks and benefits of tamoxifen and to put them into perspective. As the examples in section IV indicate, what appears to be a small reduction in the absolute risk of IBC over a 5-year period can be large compared with overall mortality risks over the same time period. Some women may be better able to understand the risks associated with tamoxifen by comparing them with the risks associated with estrogen replacement therapy (ERT). The increased risk of venous thromboembolism associated with tamoxifen is similar to that found for ERT. A pooled analysis of nine studies of the risk of venous thromboembolism with ERT revealed a risk ratio of 1.7 (95% CI = 1.0–2.9) for prospective studies and 2.4 (95% CI = 1.7–3.5) for case–control studies *(78),* similar to the risk ratio of 1.7 observed for deep vein thrombosis in the BCPT for women 50 years old or older *(1).* The risk ratio for pulmonary embolism with the current use of ERT is 2.1 (95% CI = 1.2–3.8) *(79).* Again, this is similar to the relative risk observed with tamoxifen *(1).* The absolute risk of pulmonary embolism and deep vein thrombosis is low for both tamoxifen and ERT in women under age 50 years.

Likewise, the risk of endometrial cancer associated with tamoxifen treatment is comparable to that associated with ERT. The link between endometrial cancer and the use of unopposed estrogen was postulated in 1976, when a sharp rise in incidence rates of endometrial cancer was observed in the 1970s *(80).* In a recent study, the relative risk of endometrial cancer per additional 5 years of unopposed ERT was 2.17 (95% CI = 1.91–2.47) *(81),* and higher relative risks were found for 10 or more years of unopposed estrogen use [*(28–31);* Table 4)]. When estrogen was given in combination with at least 10 days of progestin therapy or with continuous progestins *(81),* there was virtually no increased risk of endometrial cancer (relative risk = 1.07). Thus, the risk of endometrial cancer associated with tamoxifen treatment over a 5-year period is similar to that associated with the use of unopposed ERT.

The counselor should convey what is not known about the use of tamoxifen (*see* section VIII) as well as what is known. For example, the BCPT does not provide data on the effects of tamoxifen beyond 5 years, and it was not designed to study the impact of tamoxifen on total mortality, for which the relative risk was 0.81 (95% CI = 0.56–1.16). There is ongoing research to find drugs that have efficacy in reducing breast cancer risk and that are associated with fewer risks than tamoxifen, and decisions regarding the use of tamoxifen may be influenced by the potential of such research to increase management options in the future. For example, the counselor should make women aware of the Study of Tamoxifen and Raloxifene (STAR), which began in 1999.

The counselor should warn women of the need to avoid pregnancy and to rely on barrier methods of contraception while taking tamoxifen. The counselor should be aware that tamoxifen can potentiate the effects of coumarin-like anticoagulants *(82).*

An important counseling issue concerns barriers to the use of tamoxifen. The counselor and woman should discuss the costs of taking tamoxifen, including annual mammograms, annual gynecologic examinations, and the possible need for additional studies, such as pelvic ultrasound examinations or endometrial aspiration biopsies. Concerns about out-of-pocket expenses increased the chance of refusing to participate in the BCPT *(83)* and may affect the decisions of women who are not participating in clinical studies even more. Concerns about the need to discontinue ERT (*see* section VIII) may also inhibit the use of

tamoxifen *(83)*. Some women may refuse to take tamoxifen because of its unpleasant side effects, including hot flashes, irregular menses, and vaginal discharge. Another barrier is the need for long-term treatment and follow-up. The counselor and woman should recognize the challenges in their particular clinical setting to achieving long-term benefits from tamoxifen.

Finally, the counselor should assess whether the woman understands the information provided both immediately and at follow-up *(84)* and should attempt to rectify misperceptions.

VIII. Discussion

The decision to use tamoxifen to reduce the risk of breast cancer is complicated by the presence of several potential risks that must be weighed against potential beneficial effects. We have presented a methodology for determining the benefits and the risks associated with tamoxifen treatment and have provided tables that can be used to describe these risks and benefits in detail and to summarize them. These assessments are individualized by age, race, the presence or absence of a uterus, and the woman's projected 5-year risk of IBC. One can use the Breast Cancer Risk Assessment Tool developed by the Office of Cancer Communications, NCI, to estimate the projected 5-year risk of IBC based on a woman's breast cancer risk factors, and one can also estimate the projected 5-year risk of IBC from Table 2. The use of tamoxifen should not be based on a single number, such as a projected 5-year risk of IBC of 1.66%, but rather it should be based on a weighing of the various risks and benefits of tamoxifen. For older women at higher risk of endometrial cancer, stroke, and pulmonary embolism, higher levels of projected 5-year risk of IBC would be needed to justify the use of tamoxifen (Tables 10–12).

Our methods are subject to various uncertainties. Background rates (Table 3) were difficult to estimate for some types of events, such as stroke, pulmonary embolism, deep vein thrombosis, or fractures, especially in minority women. A weakness of our methodolgy is that projections for events such as stroke and pulmonary embolism depend only on age and race; it would be desirable to have validated models that included medical factors such as those in Table 4. Such models might explain much of the apparent effect of race *(36)*. In the absence of such models, it can be difficult to know whether to apply rates for stroke and pulmonary embolism from the general population, as in Tables 3, 10, and 11, or to apply the lower stroke and pulmonary embolism rates that are more appropriate for "healthy volunteers" in prevention trials (Table 12). The risk/benefit trade-off is more favorable to tamoxifen in the latter case. Our projections of breast cancer risk are less certain in black and Hispanic women than in white women (*see* section II, part A), which increases the difficulty of assessing risks and benefits in minority women.

The effects of tamoxifen were estimated mainly from white women (96.5% of the sample) in the BCPT, and our estimates of benefits for black, Hispanic, and Asian women depend on the untested assumption that the effects of tamoxifen are the same in these groups. Our conclusion that the net benefits of tamoxifen are restricted to younger black than white women (Fig. 1; Tables 10 and 11) rests on the assumption that the adverse relative risks of tamoxifen for stroke, pulmonary embolism, and deep vein thrombosis found in white women in the BCPT hold for black women, who have higher background rates of these events (Table 3). The results in Tables 10 and 11 for black women are, therefore, subject to greater uncertainty than for white women.

We have used the overall relative risk of endometrial cancer from tamoxifen in the BCPT, 2.53, to estimate the risk for women under age 50 years (Table 5). We believe that this risk estimate is more reliable than an estimate based on only the 17 endometrial cancers in the subset of women under age 50 years, for whom the relative risk was 1.21 (95% CI = 0.41–3.60). Mamounas et al. *(85)* analyzed data on the effects of tamoxifen in nine NSABP protocols for women with breast cancer. For women under age 50 years, the incidence rate of endometrial cancer per 1000 woman-years was 0.88 for women taking tamoxifen and 0.33 for women not taking tamoxifen; the corresponding relative risk was 2.65 (95% CI = 0.97–7.0). Although these combined analyses do not represent randomized comparisons and although it is possible that women taking tamoxifen were under more intense surveillance for endometrial cancer than were the other women, these data support our estimate of relative risk of 2.53 from the BCPT data. In any case, our choice of the estimate 2.53 has little effect on net benefit/risk indices because endometrial cancer is uncommon in women under age 50 years. A meta-analysis *(59)* of studies of women of all ages taking tamoxifen for about 5 years following treatment for breast cancer yielded a relative risk of 4.2 for endometrial cancer, in line with our estimate of 4.0 for women aged 50 years or more.

There is considerable debate on how best to present data on risks and benefits. Several workshop participants objected to the use of an index such as $I(1, 0.5,0)$ on the grounds that each woman has her own preferences and concerns and that no standard index would be particularly appropriate. We found, however, that broad conclusions about the net benefit of tamoxifen, such as in Fig. 1 and Tables 10 and 11, were insensitive to the particular weights used, provided they emphasized life-threatening and severe events. Moreover, we have also presented the information in considerable detail (Tables 6–8) so that women and their counselors can weigh risks and benefits using whatever weights they prefer (*see* Table 13).

There are important gaps in our knowledge that are relevant to counseling on the use of tamoxifen. The BCPT does not provide data on the long-term effects of tamoxifen because the average follow-up was 4.06 years. This lack of information and the possibility that alternative preventive agents may become available (*see* section VII) complicate the decision of when to initiate tamoxifen use. There are insufficient data on the effects of tamoxifen on overall mortality, although the results in the BCPT were encouraging in this regard (relative risk = 0.81; 95% CI = 0.56–1.16). It is unclear why two much smaller studies in Europe *(2,3)* failed to demonstrate a reduction in breast cancer risk associated with tamoxifen. It may be that differences in study populations or adherence to treatment explain these various results, and they should not be combined. If one combines the studies, however, as in section III, to obtain an overall relative risk of breast cancer of 0.59, instead of 0.50–0.51 as in the BCPT, the numbers of breast cancers expected to be prevented by tamoxifen (Table 6) are reduced by about 18%. It follows, for example, that a 45-year-old white woman with a uterus and with a projected 5-year risk of IBC of 4% would have a summary index, $I(1, 0.5, 0)$, of about 142 instead of the value of 196 in Table 10. There are also considerable uncertainties relating to the use of tamoxifen for breast cancer prevention in classes of women not included in the

BCPT, such as women with DCIS, women with small, invasive tumors, and women who have survived disease free for several years following treatment without tamoxifen for breast cancer (*see* section V).

Another issue concerns the concurrent use of hormone replacement therapy and tamoxifen. Women in the BCPT were eligible only if they took no estrogen or progesterone replacement therapy, oral contraceptive, or androgens. Forty-one percent of the women in the study reported by Powles et al. *(2)* received hormone replacement therapy, as did 14% of those in the study reported by Veronesi et al. *(3)*. Although there was no evidence from these studies that tamoxifen was less effective for women taking hormone replacement therapy than for other women, the power to detect such an interaction was small, and it remains at least a theoretical possibility that hormone replacement therapy reduces the effect of tamoxifen on breast cancer risk. Indeed, Fisher et al. *(1)* mentioned hormone replacement therapy as an important possible reason for the discrepancies in the results between the European studies *(2,3)* and the BCPT. To mimic the conditions of the BCPT as closely as possible, it is recommended that women who plan to take tamoxifen discontinue and/or refrain from taking hormone replacement therapy. In some cases, this may exacerbate hot flashes, and women may be unwilling to continue taking tamoxifen.

Much is unknown about how best to elicit a woman's concerns about specific possible adverse health outcomes and preferences regarding the use of tamoxifen. Research is also needed to define women's knowledge about their risk of breast cancer and other adverse events, about the BCPT and the effects of tamoxifen, and about the risk of breast cancer while taking tamoxifen. Studies are also needed to define effective counseling strategies and tools for conveying information on risks and benefits.

There is considerable scope for research to reduce these uncertainties and areas of ignorance. There is a need for feedback from counselors regarding the usefulness of tools such as Table 13 proposed in this article to assist in the counseling process. If such tools were thought to be useful, a computer program could be developed that would facilitate the presentation of individualized risk and benefit data such as those in Table 13 and would allow a woman to define a summary index that reflected her particular concerns regarding adverse events.

Appendix: Workshop Program and List of Participants

Program

Welcome: Barnett S. Kramer, Leslie Ford
Introduction: Richard Klausner
Breast cancer, a general review: Barbara Hulka
Risk projection models of breast cancer: Mitchell Gail, Elizabeth Claus
Endometrial cancer: Louise Brinton
Bone fractures: Joan McGowan
Cardiovascular events: Larry Friedman
Outcomes from hormone replacement therapy: Jeff Perlman
Breast Cancer Prevention Trial results: Larry Wickerham
Homogeneity of treatment effects across ages; comparison of risk and benefits in the Breast Cancer Prevention Trial: Joseph Costantino
Special considerations: Craig Jordan
Construction of quantitative risk/benefit tables : Laurence Freedman
Risk perception/communication: Russell Harris
Perspective of a high risk woman: Helene Wilson, Lonnie Williams
The counseling process: Robert Croyle
Behavioral research strategies: Barbara Rimer
Breakout Group on construction of risk/benefit analyses: Co-Chairs Joseph Costantino, Mitchell Gail
Breakout Group on risk perception/communication/counseling: Co-Chairs Robert Croyle, Russell Harris

List of Workshop Participants

Jeffrey Abrams
Julie Beitz
Jacques Benichou
Leslie Bernstein
Donald Berry
William Black
Melissa Bondy
Otis Brawley
Louise Brinton
Elizabeth Claus
Ted Colton
Joseph P. Costantino
Robert Croyle
Mary Daly
Kay Dickerson
Barbara Dunn
Bernard Fisher
Leslie Ford
Laurence Freedman
Lawrence Friedman
Mitchell H. Gail
Judy Garber
Venus Gines
Joe Harford
Russell Harris
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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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